41.001

Detecting Carbapenemase Producers in the Clinic

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Carbapenem resistance among *Klebsiella pneumoniae*, is increasing in many parts of the world, and the treatment options for such strains are very limited. The mechanisms are mainly transferable carbapenemases of K. pneumoniae carbapenemase (KPC) or metallo-betalactamase (MBL) type (mainly VIM), but also OXA-48 carbapenemases, as well as extendedspectrum beta-lactamases or AmpC in combination with porin loss. Infection control is of crucial importance for combating such resistance, and depends on adequate detection of carbapenemase-producing isolates. Several authors have reported on problems of detecting such isolates, and the reasons and possible solutions are discussed.

Carbapenem-producers have carbapenem MICs below the current clinical breakpoints of EUCAST and CLSI. However, EUCASTs epidemiological cut-offs (ECOFFs) values, the limit of the wild-type populations, have been found useful to identify such carbapenemase-producers. Disk diffusion correlates to the current MIC ECOFFs are under development, and seem to be working equally well with the tentative zone ECOFFs. In particular meropenem and ertapenem produce a good separation between wild-type isolates and carbapenem-producers. Automated antimicrobial susceptibility testing (AST) systems will in most cases detect all carbapenemaseproducers when using ECOFFs actively when reading the quantitative AST results.

Phenotypic tests for confirmation of carbapenemase-production comprise the modified Hodge test (MHT), and in-house combination disks containing carbapenems in combination with boronic acid (for KPC detection) or zinc chelators (for MBL-detection). The MHT has high sensitivity for detection of KPC, but lower for MBL. Also, there are problems with specificity, mainly with AmpC hyperproducers. The combination disk method has recently been updated with the addition of cloxacillin as a third inhibitor, in order to separate AmpC hyperproduction plus porin loss (synergy with cloxacillin and boronic acid) from KPC (synergy with boronic acid only). Further, dipicolinic acid has better specificity for MBL-detection than EDTA.

Although the above mentioned recommendations seem to identify carbapenemase-producers among *K. pneumoniae*, it is still uncertain whether they will be adequate for detection of carbapenemases in other species of Enterobacteriaceae. Further, there are still concerns regarding detection with automated AST-systems. Detection depends on the carbapenems included in the test.

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41.002

Clinical Impact and Current Epidemiology of Carbapenemase producers

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Carbapenemase-producing pathogens have become a major and increasing infectious disease threat. Their most serious impact is the lack effective therapies for the infections they cause. Given that laboratory detection is often poor, our understanding of their epidemiology is incomplete. Some types of carbapenemase producers are already ubiquitous. For other types, there are known hotspots of occurrence. KPC producers are mostly detected in the eastern USA and Israel, but have also been detected in some European and Asian countries. Metallo-β- lactamase (MBL) producers mostly occur in Asia, Europe, Australia and South America. OXAcarbapenemase have been detected worldwide. The most rapidly spreading pathogens are probably *Acinetobacter baumannii* that produce OXA carbapenemases and KPC-producing *Klebsiella pneumoniae*. However, these enzymes also occur in species that are less closely monitored, e.g. OXA-producing Enterobacteriaceae and KPC-producing *A. baumannii* and *P. aeruginosa*. There appears to be less rapid spread of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* that produce transmissible MBLs, but this observation may be a reflection of suboptimal laboratory testing rather than reality. Prompt and accurate laboratory detection is critical. Outbreaks and therapeutic failures have resulted from testing problems. Another problem is that carbapenemase producers, especially *K. pneumoniae* and *A. baumannii*, are efficient scavengers of additional resistance mechanisms and, as a consequence, are constantly changing. In this sense, they are a ''moving target'' and contemporary understandings may have reduced relevance to the therapeutic, diagnostic, and infection control challenges of the future. The current needs are for effective therapies, effective infection control based on better detection, education of health care professionals, and for research to provide better understandings of the biology of these pathogens.

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41.003

Controlling the Spread of Carbapenemase-Producing Bacteria

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Background: During 2006, Israeli hospitals faced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae*, producing the serine carbapenemase KPC-3. Locally-implemented infection control measures in affected hospitals failed to contain spread. A nationwide intervention was launched to contain the outbreak and introduce a strategy to control future dissemination of antibiotic-resistant bacteria in hospitals.

Methods: In March 2007, the Ministry of Health issued guidelines mandating physical separation of hospitalized

carriers of carbapenem-resistant Enterobacteriaceae (CRE) and dedicated staffing, and appointed a professional task force charged with containing spread of the epidemic strain. The task force paid site visits at acute care hospitals, evaluated infection control policies and laboratory methods, supervised adherence to the guidelines via daily census reports on carriers and their conditions of isolation, provided regular feedback on performance to hospital directors, and intervened additionally when necessary. During 2008, the intervention was extended to long-term care facilities, and in June 2008 national guidelines for active surveillance were issued. The primary outcome measure was the incidence of clinically diagnosed nosocomial CRE cases in acute care hospitals.

Results: By March 2007, over 1200 patients were affected in acute care hospitals. Prior to the intervention, the monthly incidence of noscomial CRE climbed steadily, peaking at over 180 cases. Crude 30-day mortality was > 30%. With the intervention, the continuous rise in incidence of CRE acquisition was halted, and at the end of the 14-month initial intervention period the number of new monthly cases was 46. Following the introduction of active surveillance guidelines, monthly incidence fell further, reaching a low of 24 as of October 2009. A direct correlation was observed between compliance with isolation guidelines and success in containment of in-hospital CRE transmission.

Conclusions: A centrally-coordinated public health intervention has succeeded in containing a nationwide outbreak of CRE in Israeli hospitals after local measures failed. The intervention demonstrates the importance of strategic planning and national oversight in combating antimicrobial resistance.

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41.004

Treatment Options for Carbapenenam Resistant Infections

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Carbapenemase producing Gram-negative bacteria (CPGN) become increasingly prevalent and cause serious infections resulting in high fatality. These organisms are resistant, not only to almost all available !-lactam antibiotics but also to other classes of agents, leaving tigecycline and colistin as the only therapeutic options. None of these agents, however, is ideal; tigecycline produces low blood levels and colistin has questionable performance in serious infections owing to poor pharmacokinetics. More worryingly, resistance to both of these compounds has been developed. The newer !-lactamase inhibitors, NXL 104 and BAL 30376, show promises for infections caused by CPGN. A proportion of carbapenemase-producing Enterobacteriacae has MICs of carbapenems within the susceptible range raising the critical question of whether carbapenems might be effective in the treatment of infections caused by such organisms.

Anecdotal reports claim microbiological and clinical response in patients infected with MBLpositive carbapenem-susceptible organisms after treatment with a carbapenem. In a prospective study of 67 patients with bloodstream infections caused by VIM-producing *K. pneumoniae*, the lowest mortality was observed in the group of patients who had received combination therapy with two active drugs, one of which was a carbapenem and the other either colistin or an active aminoglycoside, whereas therapy with one active drug resulted in a mortality similar to that observed in patients who had received therapy with no active drug. Based on this experience, it remains doubtful whether monotherapy with a carbapenem would be effective in the treatment of such infections. On the other hand, carbapenems in combination with another active agent may provide some therapeutic benefit against MBL-positive carbapenem-susceptible Enterobacteriaceae. In this respect, the issue of either reporting such isolates as fully resistant to carbapenems or consider the respective MICs at face value should remain open. In conclusion, information about how to treat infections caused by CPGN is surprisingly scarce.

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42.001

Malaria Eradication

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A global campaign to eradicate malaria in the middle of the last century relied chiefly on two powerful tools, insecticide spraying of mosquitoes to interrupt transmission and chloroquine treatment to reduce the human reservoir of infection. While this effort, led by the World Health Organization, did succeed in eliminating malaria from some areas on the edges of the malaria map, it was abandoned as a failure after little more than a decade. The emergence of insecticideresistant Anopheles mosquitoes and drug-resistant *Plasmodium falciparum* parasites, failure to understand and adapt to local differences in mosquito ecology and malaria epidemiology, and donor fatigue, all contributed to the demise of the campaign, which never included Africa, the region with by far the greatest malaria burden, then and now. In the ensuing decades, the focus shifted from eradication to control, and worldwide malaria deaths increased in the face of chloroquine resistant falciparum malaria and weak health care systems.

The development and deployment of two new tools, long-lasting insecticide-treated nets and artemisinin-based combination drug treatments, have led to dramatic reductions in malaria in several countries, including some in Africa. Malaria has even been completely eliminated recently from some endemic areas with low levels of transmission and relatively good health infrastructure. These success stories have generated such optimism that Bill and Melinda Gates and other donors and, following their lead, malariologists, are talking again about eradication. To achieve a better outcome than the first campaign, malaria eradicators in the 21st century will need to learn and apply lessons from both past and recent failures and successes. If a renewed malaria eradication effort is started with the tools in hand now, it will be essential to keep the pipeline